Symptom onset and treatment in acute myocardial infarction

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CHAPTER 6

Role and timing of coronary intervention in non-ST-elevation myocardial infarction

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Part 2 - Symptom Onset to Treatment

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Abstract

Non-ST-elevation myocardial infarction (NSTEMI) has become the most common presentation of acute myocardial infarction. Its treatment is challenging and often less straightforward as compared with ST-elevation myocardial infarction (STEMI). First, clinicians must decide whether an initial invasive or an initial conservative treatment is appropriate for their NSTEMI patient. If an invasive strategy is chosen, subsequent decisions on the optimal timing of coronary angiography and possible intervention have to be made. Both aggressive and conservative strategies have their own potential risks and benefits. Aggressive strategies may result in more procedural complications, which is especially unwanted in patients otherwise at low risk of events. In contrast, conservative strategies may be harmful in high-risk patients who benefit most of early reperfusion therapy. We aim to discuss the evidence base of this decision process where risk stratification is of paramount importance with the goal of obtaining the optimal outcome for the individual patient.

Introduction

With an estimated incidence of 150-200 per 100,000 in the United States, non-ST-elevation myocardial infarction (NSTEMI) represents the most common presentation of acute myocardial infarction. Its usual cause is atherosclerotic plaque rupture or erosion and formation of a non-occlusive thrombus in a coronary artery, although other conditions that cause a supply/demand imbalance to the myocardium may also cause NSTEMI (e.g. coronary spasm or dissection or severe anemia). With the introduction of troponin assays the last decade has seen an increase in the incidence of NSTEMI, while the incidence of ST-elevation myocardial infarction (STEMI) has simultaneously decreased. That the improved sensitivity to diagnose NSTEMI does not necessarily result in additional identification of low-risk NSTEMI patients is reflected in a contemporary Swedish study. In this nationwide analysis no improvement in 1-year survival of NSTEMI patients was seen in between 1990 and 2010, while STEMI patients did show improved survival. In an analysis from the Global Registry of Acute Coronary Events (GRACE), 6-month outcome in NSTEMI patients did show a modest improvement between 1999 and 2005, but this was only after adjustment for the worsening baseline risk-profile that was seen over time in NSTEMI patients. Thus, diagnosis, risk
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stratification, and treatment of NSTEMI continues to be a major challenge in the upcoming decade and is often less straightforward than in STEMI. We aim to give an overview of the role and timing of coronary intervention and the importance of risk stratification in selecting an appropriate treatment strategy in patients with NSTEMI.

Risk stratification

Before estimating risk in a NSTEMI patient and deciding on if and when to take a patient to the cardiac catheterization lab, one needs to question what the possible scenarios in terms of presentation, angiographic findings, and invasive management may be. First, it is important to note that approximately 4% of NSTEMI patients present with cardiogenic shock upon admission. This is a population with an exceedingly high mortality rate (higher than in STEMI patients presenting with cardiogenic shock) and is unlikely to be represented in major clinical trials. In the 2005 GRACE registry, in-hospital invasive management in NSTEMI patients consisted of angiography in 62.6% of cases with 34.6% of patients undergoing subsequent percutaneous coronary intervention (PCI) and 5.1% of patients undergoing coronary artery bypass grafting (CABG). These rates were 76.2% for angiography, 43.6% for PCI, and 11.5% for CABG in the 2009 results of the US National Cardiovascular Data Registry. At the time of angiography, between 9% and 14% of patients with NSTEMI do not have a coronary stenosis ≥50%. Typical findings in NSTEMI patients with significant coronary artery disease are single vessel disease in 40-45%, 2-vessel disease in 25-30%, 3-vessel disease in 15-22%, and left main disease in 6-13%. Approximately 20% of NSTEMI patients with angiographically significant coronary artery disease are managed medically. These patients more often have a history of (extensive) coronary artery disease with prior interventions and have a poorer outcome. In addition to clinical judgment, several validated multivariable risk models are available to estimate the risk of adverse outcome in NSTEMI patients. This risk estimation is of great importance since it will guide the subsequent treatment strategy as is discussed later. American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of the GRACE, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), or Thrombolysis In Myocardial Infarction (TIMI) risk models in patients with suspected acute coronary syndrome (Class IIaB). The European Society of Cardiology (ESC) guidelines mainly refer to the GRACE score to estimate prognosis and the “Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes
with Early implementation of the ACC/AHA guidelines” (CRUSADE) risk score to estimate bleeding risk (Class IB). Clinical characteristics considered by these risk scores are summarized in Table 1. The GRACE score was developed from a large ongoing intercontinental registry of patients with acute coronary syndromes. Risk models are available that predict in-hospital or 6-month death or death or myocardial infarction. The 6-month risk estimates can be calculated both upon admission and at discharge. The commonly used GRACE risk model that estimates the 6-month risk of death or myocardial infarction upon admission was developed among 21,688 GRACE patients and had a c-statistic of 0.73 in the initial validation cohort (the c-statistic for 6-month mortality alone was 0.81). Due to its complexity, the GRACE score requires digital calculation. Nonetheless, it is widely used and has been validated extensively. The GRACE score is accessible online at http://www.outcomes-umassmed.org/grace/. The PURSUIT risk score was developed among 9461 participants of the PURSUIT trial testing eptifibatide (Integrilin) versus placebo in patients with acute coronary syndrome without persistent ST-elevation. The PURSUIT risk score predicts 30-day death (initial c-statistic 0.80) and death or myocardial infarction (initial c-statistic 0.66) by using a scoring scheme and has been subjected to external validation. The TIMI risk score estimates 14-day risk of mortality, new or recurrent myocardial infarction, or severe recurrent ischemia requiring urgent revascularization and is an easy to memorize risk score where 1 point is awarded for each characteristic. It was developed in 1957 patients with unstable angina or NSTEMI receiving unfractionated heparin in the TIMI 11B trial (testing enoxaparin vs. unfractionated heparin) and has subsequently been validated by the TIMI investigators (c-statistic of 0.59-0.65) and others. The TIMI risk score is available at http://www.timi.org/. Studies comparing the GRACE, PURSUIT, and TIMI risk scores have concluded that the GRACE score yields the best predictive power. The CRUSADE bleeding score can be calculated to estimate in-hospital major bleeding risk in patients with NSTEMI, which may have consequences in selecting anticoagulant and antiplatelet therapy. The CRUSADE score was developed in 71,277 patients enrolled in the US CRUSADE quality improvement initiative and has been validated both within the CRUSADE registry (c-statistic 0.70) and externally. It works with a scoring chart that is hard to memorize but can be calculated at http://www.crusadebleedingscore.org/. With regard to risk stratification, the importance of age must be stressed.
In the PURSUIT risk score, age ≥70 years is awarded more risk points than any other characteristic including heart failure and abnormalities on the admission electrocardiogram (ECG).\textsuperscript{21} Similarly, age ≥65 years was associated with the highest odds ratio for adverse outcome in the development cohort of the TIMI risk score\textsuperscript{23} and age (per decade increase) and cardiac arrest represented the highest hazard ratio for death at 6 months in the GRACE risk model beyond ST-deviation and cardiac biomarker elevation.\textsuperscript{18} Age is not included in the CRUSADE bleeding score, but may already be accounted for in the Cockcroft-Gault creatinine clearance calculation.\textsuperscript{26} The usage of risk models greatly enhances the ability to differentiate between low- and high-risk patients and their use should be part of the daily clinical routine. Although there is no question about the importance of clinical judgment in individual cases, it has recently been shown that the GRACE score outperforms physician-perceived risk in terms of prognostic accuracy in aggregate analysis.\textsuperscript{28} Nonetheless, it is important
to be aware of the limitations of risk models. With c-statistic values typically reported around 0.60 to 0.85,20 the aforementioned risk models show moderate to excellent – but not perfect – discriminatory capacity in terms of separating patients with and without adverse outcome. Efforts to further improve risk scores by adding biomarkers have been successfully attempted, such as addition of N-terminal pro-brain natriuretic peptide (NT-proBNP) to the TIMI risk score29 and addition of NT-proBNP or growth differentiation factor-15 to the GRACE risk score.30 However, these strategies are associated with additional costs for biomarker assessment and have not (yet) been adopted into broad clinical practice. Finally, new risk scores incorporating clinical, laboratory, and angiographic characteristics have been developed in the light of the increasing use of early angiography and PCI in patients with acute coronary syndromes.31,32 These later risk scores which include angiographic characteristics may better predict in-hospital and long-term outcome after PCI. They are however limited and not suitable to determine the optimal initial treatment strategy upon admission.

THE ROLE OF CORONARY INTERVENTION

General concept
Coronary revascularization strategies in NSTEMI are summarized in Box 1. The initial conservative strategy consists of observation and stabilization by institution of at least a beta blocker, an anticoagulant, and dual antiplatelet therapy. If medical therapy succeeds, the patient usually undergoes a non-invasive stress test before discharge. The patient will proceed to coronary angiography if medical therapy fails (i.e. if the patient develops refractory or recurrent angina) or in case of a high-risk stress test result. A potential advantage of this strategy is that initial stabilization and pretreatment with anticoagulant and antiplatelet agents may result in lower periprocedural complications in patients that do proceed to angiography as compared with the initial invasive strategy (Figure 1). Furthermore, it may reduce the use of angiography with its associated costs and risks in low-risk patients and allows for a more thorough clinical assessment and recognition of (latent) comorbid conditions.

In the initial invasive strategy, patients routinely undergo coronary angiography within 72 hours. Its potential benefit is evident in patients that are considered to be at high-risk of adverse outcome upon admission. In these patients, timely angiography and intervention may prevent ischemic events otherwise occurring during the ‘observation and stabilization’ period in the conservative strategy (Figure 1). However, even in stabilized
intermediate-risk patients, the initial invasive strategy can be seen as an effective method of risk stratification since it provides clarity with regard to coronary anatomy. It can identify patients with a high-risk coronary anatomy in an early phase regardless of adequate classification by risk models, such as patients with 3-vessel or left main disease amenable for CABG and patients with a proximal left anterior descending artery (LAD) lesion suitable for PCI. Finally, it may reduce length of hospitalization and occurrence of rehospitalization regardless of angiographic findings.\textsuperscript{14,15}

**Conservative versus invasive strategy**

The first randomized trial comparing an invasive and conservative strategy was conducted in the early 90’s,\textsuperscript{33} but current guidelines and contemporary meta-analyses have mainly focused on trials conducted in the stent era (Table 2). This will also be the focus of our overview (in chronologic order). Notably, most trials were conducted in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) and therefore also included patients with unstable angina. Key baseline and procedural characteristics differed substantially between the trials (Table 2).

The Scandinavian multicenter FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) trial randomized 2457 patients with NSTE-ACS to an initial invasive strategy versus an initial conservative strategy.\textsuperscript{9} In the invasive group 98% of patients underwent coronary angiography after a median of 4 days, versus 47% after a median of 17 days in the conservative group. Subsequent treatment is listed in Table 2. After an initial hazard for the invasive group in the first 2 weeks, the primary endpoint of the trial – a composite of death and myocardial infarction at 6 months – was reached in 9.4% in the invasive group versus 12.1% in the conservative group (P=0.031). This was mainly driven by a difference in myocardial infarction rather than

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**Box 1. Coronary revascularization strategies**

| Initial conservative strategy (selective invasive) – angiography is only performed in case of: |
| Hemodynamic or electrical instability; |
| Refractory or recurrent angina despite optimal medical therapy; |
| Dynamic ECG changes; |
| High-risk stress test results. |
| Initial invasive strategy (routine invasive) – routine angiography within 72 hours of presentation |
| **Urgent** – within 2 hours of presentation |
| **Early (nonurgent)** – after 2 hours but within 24 hours of presentation |
| **Delayed** – after 24 hours but within 72 hours of presentation |

ECG, electrocardiogram.
120

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18 trial, 2220 NSTE-ACS patients were randomized to an initial invasive strategy versus an initial conservative strategy.\textsuperscript{35} A major difference with the FRISC-II trial was the substantially higher use of glycoprotein IIb/IIIa inhibitors in patients undergoing PCI. Patients in the TACTICS-TIMI 18 trial underwent invasive procedures earlier during index hospitalization with 97% of patients in the invasive group undergoing angiography after a median of 22 hours compared with 51% in the conservative group after a median of 3 days. The primary endpoint of the trial was a composite of death, myocardial infarction, or rehospitalization for an acute coronary syndrome at 6 months, and occurred in 15.9% of patients assigned to the invasive strategy versus 19.4% assigned to the conservative strategy (P=0.025). Also in this trial, there were no differences in death: the composite endpoint was mainly driven by differences in the occurrence of myocardial infarction and rehospitalization (Table 2). Of note, the invasive strategy was at the...
Table 2. Randomized trials on initial invasive versus initial conservative revascularization strategies

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<td>Cons. (n=1235)</td>
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<td>Cons. (n=1106)</td>
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<td>65*</td>
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<tr>
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<td>12.1§</td>
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<td>10.1§</td>
<td>4.8§</td>
<td>6.9§</td>
<td>3.1§</td>
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<td>% Rehospitalization</td>
<td>31§</td>
<td>49§</td>
<td>11.0</td>
<td>13.7</td>
<td>9.4</td>
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*median age; †ST-deviation; ‡rate at 1 year; §P<0.05 between invasive and conservative group; CABG, coronary artery bypass grafting; GPI, glycoprotein IIb/IIIa inhibitor; N/A, not available; PCI, percutaneous coronary intervention.

W/stent indicates dual antiplatelet therapy in stented patients only, usually ≤1 month. In the ICTUS trial dual antiplatelet therapy was also prescribed more routinely.
expense of a higher overall bleeding rate (5.5% vs. 3.3%; P<0.01) although TIMI major bleeding was similar (1.9% vs. 1.3%; P=0.24). Hospitalization was 1 day shorter in the invasive group.

With 131 patients, the Czech Value of First Day Coronary Angiography/ Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction: An Open Multicenter Randomized Trial (VINO) was a considerably smaller trial comparing an invasive versus a conservative strategy in a high-risk population of only NSTEMI patients. The VINO trial was successful with regard to its ambition to offer early procedures in the invasive group; the mean time to angiography was 6.2 hours versus 61 days in the conservative group and the mean time to PCI was 8.6 hours versus 55 days, respectively. The occurrence of the primary endpoint – death or myocardial infarction at 6 months – was 6.3% in the invasive group and 22.4% in the conservative group (P<0.001). In this trial a 6-month mortality benefit in favor of the invasive group was found (3.1% vs. 13.4%; P=0.030). This finding may be explained by the high risk profile of the included patients.

The Randomized Intervention Trial of unstable Angina (RITA)-3 was a British multicenter trial that randomized 1810 NSTE-ACS patients to an initial invasive versus an initial conservative strategy. In contrast to the other studies, the presence of elevated cardiac biomarkers was not an inclusion criterion. Indeed, patients with creatine kinase (CK) or CK-MB elevations higher than twice the upper limit of normal were even excluded, resulting in a relatively low-risk study population (Table 2). Patients in the invasive group underwent angiography during the initial hospitalization after a median of 2 days compared with an in-hospital angiography rate of 16% in the conservative group. The co-primary endpoints of the trial were a composite of death, myocardial infarction, or refractory angina warranting re-admission at 4 months and death or myocardial infarction at 1 year. At 4 months, the primary endpoint occurred in 9.6% of patients in the invasive group versus 14.5% of patients in the conservative group (P=0.001). However, this difference was entirely driven by a 50% reduction in refractory angina in the invasive group and no significant differences were seen in death or myocardial infarction at 4 months or 1 year follow-up (Table 2). In-hospital bleeding occurred in 8% in the invasive group and 4% in the conservative group. In the invasive group, patients used fewer antianginal agents at 1-year follow-up. It has been argued that the lack of reduction in myocardial infarction with invasive management seen in RITA-3 as compared with the FRISC-II and TACTICS-TIMI 18 trials may at least be partially explained by
their different definitions of myocardial infarction. FRISC-II and TACTICS-TIMI 18 both used different definitions for spontaneous and periprocedural myocardial infarction of which the definition of spontaneous myocardial infarction was more sensitive. As a consequence, a greater proportion of the patients in the conservative group was exposed to a more sensitive definition of myocardial infarction. In contrast, the same definition for spontaneous and periprocedural myocardial infarction was used in RITA-3.

The final trial in this field was the multicenter Dutch Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial. In this trial, a relatively high-risk population of 1200 NSTEMI patients with elevated troponin T levels were randomized to an initial invasive strategy versus an initial conservative strategy. The median time to PCI was 23 hours in the invasive group and 11.8 days in the conservative group. There was a high use of glycoprotein IIb/IIIa inhibitors, although more frequently so in the invasive group (Table 2). The primary endpoint of the trial consisted of 1-year death, myocardial infarction, or hospitalization for angina. This occurred in 22.7% of patients in the invasive group and 21.2% of patients in the conservative group (P=0.33). The (remarkably low) rate of death was the same in both groups (2.5%), and while rehospitalization rates were significantly lower in the invasive group, an unexpected excess in myocardial infarction was seen (Table 2). The later was solely the consequence of a more than twofold higher rate of PCI and CABG related myocardial infarction in the invasive group (11.3% vs. 5.4%; P=0.001). The rate of in-hospital major bleeding was 3.1% in the invasive group and 1.7% in the conservative group. The findings of the ICTUS trial may be explained by routine monitoring of cardiac biomarkers after each PCI procedure (resulting in a higher rate of periprocedural myocardial infarction in the invasive group) on the background of a more advanced pharmacological treatment strategy including high-dose statins and dual antiplatelet therapy with clopidogrel (limiting the event rate in the conservative group). Additionally, the ICTUS investigators have shown that actual in-hospital revascularization was associated improved outcome. This may well explain the lack of benefit for the invasive strategy in the intention-to-treat analyses, since the rate of in-hospital revascularization was relatively high in the conservative group (40%) as compared with the invasive group (76%).

Several meta-analyses have been published on the topic of invasive versus conservative treatment strategies in NSTE-ACS. One particularly meticulous meta-analysis was conducted by Hoenig et al.
This study-level meta-analysis also considered additional follow-up from the FRISC-II,\textsuperscript{34,41,42} RITA-3,\textsuperscript{43} and ICTUS trials.\textsuperscript{44} No additional follow-up was available in TACTICS-TIMI 18 and VINO. Its principal findings were that the invasive strategy was not associated with a mortality benefit at any time point (in-hospital: relative risk 1.53, 95% confidence interval [CI] 0.98-2.39; 4-5 years: relative risk 0.90, 95%CI 0.76-1.08) as compared with the conservative strategy and was associated with an increased risk of periprocedural myocardial infarction and bleeding. The invasive strategy did, however, reduce the incidence of myocardial infarction during intermediate and long-term follow-up (3-5 years: relative risk 0.78, 95%CI 0.67-0.92). Furthermore, the invasive strategy reduced the early and intermediate occurrence of refractory angina and early and intermediate but not late rehospitalization rates. In summary, the invasive strategy seems to reduce the long-term occurrence of myocardial infarction at the expense of a higher rate of early complications in NSTE-ACS patients. Still, one revascularization strategy does not confer a survival benefit over the other in a trial population. Observational studies have shown that an invasive strategy may safely be performed in a more general population,\textsuperscript{45-47} although a recent report emphasized that intraprocedural complications are common in the invasive strategy and adversely affect prognosis.\textsuperscript{48} Therefore, risk stratification and consideration of specific subgroups is needed to effectively balance the early procedure related hazard of an invasive strategy against the risk of ischemic events in the conservative strategy.

**Risk stratification and treatment selection**

A systematic approach to risk stratification should be used upon admission to increase awareness of the guideline recommendations and help guide treatment selection while avoiding some common pitfalls. First, NSTE-ACS patients with refractory angina or hemodynamic or electrical instability should be selected for an invasive strategy whenever possible, since these patients are at very high risk of ischemic events. This is also reflected in international guideline recommendations (ACC/AHA Class IB; ESC Class IC).\textsuperscript{14,15} Second, a well-validated multivariable clinical risk score should be calculated and patients with a high baseline risk should be considered for an invasive strategy (ACC/AHA and ESC Class IA).\textsuperscript{14,15} The hypothesis of a baseline risk dependent benefit from an invasive strategy was elegantly tested in a collaborative meta-analysis\textsuperscript{49} that included patient-level data and 5-year follow-up from the FRISC-II,\textsuperscript{42} RITA-3,\textsuperscript{43} and ICTUS trials.\textsuperscript{50} In this analysis, the authors
demonstrated that high-risk patients benefit most of an invasive strategy in terms of reduction of cardiovascular death or myocardial infarction (Figure 2). A prespecified subgroup analysis of the TACTICS-TIMI 18 trial also favored an invasive strategy in patients with an intermediate and high TIMI risk score, although the interaction was non-significant. Further analysis by the British National Institute for Health and Care Excellence (NICE) showed that these trial results are obtained in a population that does not include the patients at highest risk in clinical practice. Thus, the actual benefit from an invasive strategy in high-risk patients among the general population may even be greater. Selection of an invasive strategy in low-risk patients is discouraged by current guidelines (ACC/AHA Class IIIC, ESC Class IIIA). A key issue in the context of risk stratification and revascularization strategy selection is the so called “treatment-risk paradox”. This refers to the observation that invasive management is more common in lower risk patients and often denied in high-risk patients in clinical practice; a pattern that opposes guideline recommendations and the evidence-based clinical benefit patients are expected to derive from such interventions. This observation

Figure 2. Five-year cumulative incidence of cardiovascular death or myocardial infarction by interventional strategy in a patient-level meta-analysis of the FRISC-II, ICTUS, and RITA-3 trials. The figure clearly shows that high-risk patients gained most benefit from a routine invasive (initial invasive) strategy (n=709; risk difference −11.1%; 95% confidence interval −18.4% to −3.8%) as compared with intermediate-risk (n=1832; risk difference −3.8%; 95% confidence interval −7.4% to −0.1%), and low-risk patients (n=2926; risk difference −2.0%; 95% confidence interval −4.1% to 0.1%; interaction p<0.0001). A study specific risk score was calculated for this analysis which considered age, diabetes, prior myocardial infarction, ST-depression, hypertension, and body mass index <25 or ≥35 to be high-risk features. Reprinted from with permission from Elsevier.
seems to reflect an unwanted risk-averse strategy to coronary intervention, as it cannot be fully explained by confounding factors such as comorbidities. Another pitfall in risk estimation and treatment selection concerns cardiac biomarkers. Current guidelines mention that an invasive approach should be considered in patients with elevated cardiac biomarkers (mostly troponin).\textsuperscript{14,15} Indeed, an elevated troponin level is a high-risk feature (Table 1) and the idea of a single high-risk marker is attractive. However, the prognostic value of an elevated troponin level as a single variable is low and inferior to a multivariable risk score.\textsuperscript{53,54} This is underscored by the results of the ICTUS trial, where all patients had elevated troponin levels but no benefit for an invasive strategy could be demonstrated.\textsuperscript{38}

Subgroups and treatment selection

Although treatment selection should principally be based on multivariable baseline risk, the findings in a number of specific subgroups are worth mentioning. Several studies have assessed elderly patients. In the Italian Elderly ACS trial 313 NSTE-ACS patients ≥75 years were randomized to an invasive versus a conservative strategy.\textsuperscript{55} The primary endpoint, a composite of death, myocardial infarction, disabling stroke, and rehospitalization for bleeding or cardiovascular causes at 1 year, occurred in 27.9% of patients assigned to the invasive versus 34.6% of patients in the conservative group (P=0.26). However, an invasive strategy was beneficial to patients with elevated troponin (hazard ratio 0.43, 95%CI 0.23-0.80; P-interaction=0.03). As can be expected from their higher baseline risk, several large observational studies\textsuperscript{56,57} and a recent meta-analysis of clinical trials\textsuperscript{58} have also suggested benefit from an invasive strategy in elderly NSTE-ACS patients. Unfortunately, age seems to be particularly susceptible to the treatment-risk paradox resulting in underutilization of invasive management of these patients.\textsuperscript{56} Clearly, comorbidities and patient preference for a conservative strategy should be considered,\textsuperscript{14,15} but in their absence advanced age alone should not be an argument for selection of a conservative treatment strategy.\textsuperscript{59} Benefit from an invasive over a conservative strategy in elderly patients with comorbidities is subject of a small ongoing clinical trial (NCT01645943).\textsuperscript{205} Women typically represented one quarter to one third of the trial population (Table 2). In a randomized substudy of the Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS)-5 trial 92 women with NSTE-ACS were
assigned to an invasive strategy and 92 women were assigned to a conservative strategy. The primary endpoint, death, myocardial infarction or stroke at 2 years, showed a non-significant difference between the invasive (21%) and conservative (15.4%) strategy. However, major bleeding was more frequent in the invasive group and there was a trend towards higher 2-year mortality (8.8% vs. 2.2%, hazard ratio 4.65, 95%CI 0.97-22.20). The investigators also combined their findings with the sex-specific results of previous trials in a meta-analysis yielding 2692 women. They observed significant sex-specific heterogeneity with no apparent benefit from the invasive strategy in terms of 6- to 12-month death or myocardial infarction (odds ratio 1.18, 95%CI 0.92-1.53) or death (odds ratio 1.51, 95%CI 1.00-2.29) in women, while this benefit was seen in men. However, these results should be interpreted with caution in the absence of a large clinical trial in women.

Benefit from an invasive strategy in diabetics was assessed in a study-level meta-analysis of clinical trials that included 9904 patients (18% diabetics). The authors found that the risk of 1-year death, myocardial infarction, and rehospitalization for an acute coronary syndrome showed a non-significant trend favoring the invasive strategy with similar results in diabetic and non-diabetic patients. An invasive strategy did appear to result in fewer nonfatal myocardial infarctions at 1-year follow-up in diabetic patients (relative risk 0.71, 95%CI 0.55-0.92) but not in nondiabetic patients (relative risk 0.98, 95%CI 0.74-1.29). The study included both pre-stent era and stent era studies but the authors noted that their results would have been similar if they had only included stent era trials. Given these findings, it is reasonable to state that an invasive strategy should be more accessible to diabetic patients.

Another subgroup that should be considered for an initial invasive strategy are patients exhibiting a characteristic ECG pattern with precordial T-wave inversion, also known as Wellens’ syndrome. These patients often have a critical proximal LAD stenosis and may be at risk of a large anterior myocardial infarction if managed conservatively. Similarly, echocardiographic assessment of left ventricular function and mitral regurgitation may help to select patients for an invasive strategy, since compromised left ventricular function (<40%) suggests possible presence of left main or 3-vessel disease amenable for CABG and presence of grade 2-4 mitral regurgitation may be associated with adverse outcome if invasive management is delayed. Furthermore, guidelines recommend to consider an invasive strategy in patients with overt heart failure,
recent PCI, or prior CABG. These patients were largely excluded in the revascularization strategy trials.

**TIMING OF CORONARY INTERVENTION**

**Delay to reperfusion in NSTEMI**

In the interval between symptom onset and reperfusion therapy several factors can be identified in patients with NSTEMI that are especially complicating compared with STEMI patients. First, NSTEMI patients tend to have a longer prehospital delay, and are less likely to use emergency medical services. Certainly, a short time to first medical contact is desirable to facilitate expeditious diagnosis and early pharmacological therapy and to treat possible life-threatening complications such as arrhythmia or cardiogenic shock. Second, while 12-lead ECG based prehospital triage has shown to contribute to early diagnosis and treatment in STEMI patients, this is not the case in NSTEMI patients who also require (in-hospital) cardiac biomarker assessment for diagnosis. Finally, whereas delay to reperfusion should be as short as possible to optimize outcome in STEMI patients, the relation between delay to reperfusion and outcome in NSTEMI is more complex. In the last decade, several trials have assessed the optimal timing of coronary intervention in NSTEMI patients. It is useful to subdivide these into trials comparing early versus delayed intervention and trials comparing urgent versus early intervention (Box 1).

**Early versus delayed invasive management**

The international Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial is by far the largest trial that has addressed the timing of angiography in NSTEMI patients selected for an invasive strategy. It assigned patients to early angiography within 24 hours (n=1593; median delay 14 hours) versus delayed angiography after 36 hours (n=1438; median delay 50 hours). In the early group, PCI was performed in 59.6% and CABG in 14.8% of patients. These rates were 55.1% for PCI and 13.6% for CABG in the delayed group. The primary endpoint of the trial was a composite of 6-month death, myocardial infarction or stroke and occurred in 9.6% in the early group and 11.3% in the delayed group (P=0.15). However, in a prespecified analysis there was a significant interaction between the primary endpoint and patient baseline risk, suggesting significant benefit from early intervention in high-risk patients with a GRACE score >140 (hazard ratio 0.65; 95%CI 0.48-0.89) as compared with patients with a GRACE score ≤140 (hazard ratio 1.12; 95%CI 0.81-1.56; P-interaction=0.01).
Furthermore, early intervention was associated with a lower rate of refractory ischemia at 30 days and 6 months (1.0% vs. 3.3% at 6 months; P<0.001). Bleeding rates were similar in both groups. The findings of the TIMACS trial have mainly driven the current guideline recommendations, stating that an invasive strategy should be instituted within 12 to 24 hours (ACC/AHA Class IIaB) or 24 hours (ESC Class IA) of admission in stable high-risk patients.\textsuperscript{14,15}

The oldest study that has addressed the timing of angiography in NSTE-ACS patients is the Early or Late Intervention in unStable Angina (ELISA) trial.\textsuperscript{73} In this pilot trial 220 patients were randomized to early angiography (n=109; median delay 6 hours) versus late angiography (n=111; median delay 50 hours). Only patients in the late angiography group were pretreated with a glycoprotein IIb/IIIa inhibitor. Revascularization rates in the early and late group were 61% versus 58% for PCI and 14% versus 19% for CABG. The primary endpoint of the trial was the enzymatic infarct size, which was in favor of the late group (lactate dehydrogenase area under the curve 629 U/l vs. 432 U/l; P=0.02). However, it is uncertain which part of this benefit may be attributed to timing of intervention since glycoprotein IIb/IIIa inhibitor use also differed between the trial arms. No differences in clinical events were seen in this single center pilot trial (30-day death or myocardial infarction 9.2% vs. 9.0%; P=0.97).

The multicenter German Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) trial aimed to compare early angiography (n=203; median delay 2.4 hours) with a prolonged cooling-off period of at least 3 days before angiography (n=207; median delay 86 hours) in NSTE-ACS patients.\textsuperscript{74} Subsequent treatment consisted of PCI (70.4% vs. 64.3%) and CABG (7.9% vs. 7.7%) in the early and cooling-off group, respectively. The primary endpoint of the trial was death or myocardial infarction at 30 days, and occurred in 5.9% in the early group versus 11.6% in the cooling-off group (P=0.04). These results were mainly driven by a higher rate of myocardial infarction during the cooling-off period (10.1% vs. 5.9%; P=0.12). Thus, a prolonged cooling-off period in patients selected for an invasive strategy seems both impractical and hazardous.

The recently published Dutch multicenter ELISA-3 trial randomized a relatively high-risk NSTE-ACS population (median GRACE score 135) to early angiography (n=269; median delay 2.6 hours) versus delayed angiography (n=265; median delay 54.9 hours).\textsuperscript{75} Revascularization rates were 66.7% versus 61.9% for PCI and 23.2% versus 25.7% for CABG in the early and delayed groups, respectively. The primary endpoint of this trial was
defined as death, reinfarction, or recurrent ischemia at 30-days and was expected to have an incidence of 25%. However, it occurred in 9.9% in the early group versus 14.2% in the delayed group (P=0.135), mainly driven by a trend towards lower recurrent ischemia in the early group (7.6% vs. 12.6%; P=0.058). Hospitalization was 2 days shorter in the early group. The finding of a 30% relative risk reduction in the primary endpoint with an early invasive strategy in the high-risk population included in ELISA-3 seems to be in accordance with the findings of the TIMACS trial and we argue that lack of statistical significance should be seen in the light of the lower than expected event rate. Finally, 2 small single center trials randomized NSTEMI patients to an early invasive versus a delayed invasive strategy. Both of the trials found better outcomes in patients treated with an early invasive strategy, although neither had defined a primary endpoint.\textsuperscript{76,77}

**Urgent versus early invasive management**

Three trials have compared urgent (<2 hours) and early invasive strategies.\textsuperscript{78-80} The first study to do so was the Optimal Timing of Coronary Intervention in Unstable Angina (OPTIMA) trial.\textsuperscript{78} This trial assessed timing of PCI rather than angiography and therefore only included NSTE-ACS patients eligible for PCI. Patients were randomized to urgent PCI (n=73; median delay 30 minutes) versus early PCI (n=69; median delay 25 hours). The trial aimed to include 566 patients, but was terminated prematurely due to recruitment challenges. Nonetheless, the trial reached its primary endpoint; a composite of 30-day death, myocardial infarction, and unplanned revascularization was seen in 60% of patients in the urgent group versus 39% of patients in the early group (P=0.004). Notably, there were no deaths and the difference was primarily driven by excess myocardial infarction in the urgent group (60% vs. 38%; P=0.005) which was defined as CK-MB above the upper limit of normal.

The Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) trial randomized 352 NSTE-ACS patients with a TIMI risk score ≥3 to urgent angiography (n=175; median delay 1.2 hours) versus early angiography (n=177; median delay 20.8 hours) across multiple French centers.\textsuperscript{79} PCI was performed in 80.1% of patients in the urgent group versus 69.5% in the early group. These rates were 11.0% versus 11.3% for CABG. The primary endpoint of the trial was enzymatic infarct size and did not show any difference between the urgent and early group (median peak troponin I 2.1 ng/ml vs. 1.7 ng/ml; P=0.70). And although the composite clinical
endpoint of 1-month death, myocardial infarction or urgent revascularization was similar in both groups (13.7% vs. 10.2%; \(P=0.31\)), there was a trend towards a higher incidence of myocardial infarction in the urgent group (9.1% vs. 4.5%; \(P=0.09\)).

Finally, the German multicenter Leipzig Immediate versus early and late Percutaneous coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI) trial randomized high-risk NSTEMI patients (median GRACE score approximately 137) to 3 different treatment strategies: 1) urgent invasive (n=200); 2) early invasive (n=200); 3) initial conservative (n=200). In the urgent invasive group, median time to angiography was 1.1 hour, PCI was performed in 76% of patients, and CABG in 8% of patients. In the early invasive group, median time to angiography was 18.3 hours and revascularization rates were 71% for PCI and 13% for CABG. In the conservative group the angiography rate was high with 85% of patients undergoing angiography after a median of 67.2 hours with subsequent PCI in 57% and CABG in 13%. The trial was neutral with regard to enzymatic infarct size, its primary endpoint (median peak CK-MB 0.94 μkat/l for urgent invasive, 0.78 μkat/l for early invasive, and 0.91 μkat/l for initial conservative; \(P=0.18\)). However, at 6-month follow-up, the urgent strategy was associated with a higher rate of nonfatal myocardial infarction (urgent 16.5%; early 10.0%; conservative 8.0%; \(P=0.02\)), while the early and conservative strategy were associated with a higher rate of refractory ischemia (urgent 0%; early 6.5%; conservative 10.0%; \(P<0.001\)). Hospital stay was 1 day shorter in the urgent and early groups. Bleeding was similar across all groups.

The conclusions of observational studies assessing timing of intervention have varied widely, reporting on benefit,\(^{81}\) equal outcome,\(^{82}\) or harm\(^{83}\) associated with an early versus delayed invasive strategy. These discordant findings should be seen in the light of the limited ability of observational studies to untangle the clinical impact of treatment strategies that allow for cross-over under certain conditions (e.g. earlier treatment in case of hemodynamic instability).\(^{39}\) The observational studies could only adopt an as-treated approach, since none of them were primarily designed to assess the timing of treatment and the intentions of the operator on admission were not recorded. Nonetheless, the results of the trials on timing of coronary intervention have shown that a delayed invasive strategy is hazardous compared with an early invasive strategy in high-risk NSTE-ACS patients (e.g. ISAR-COOL, TIMACS). With a total patient number of 894 in all trials combined, the body of evidence comparing urgent invasive with early invasive management is considerably smaller. Even so, all 3 trials in this field have consistently shown a higher rate of myocardial
infarction in the urgent invasive group. Based on these observations, both urgent (<2 hours) and delayed invasive (>24 hours) strategies may be associated with adverse outcome. Meta-analyses on timing of intervention to date have mostly compared earlier with later intervention (with the exception of a sensitivity analysis comparing <20 and ≥20 hours) and therefore have not shown any significant differences in terms of death or myocardial infarction. However, we demonstrate in an exploratory analysis that significant differences in the incidence of myocardial infarction can be appreciated when urgent, early, and delayed management are analyzed separately (Figure 3). A large clinical trial (similar or larger than the TIMACS trial) comparing urgent with early invasive management in high-risk NSTE-ACS patients seems warranted, but we are only aware of 2 modestly sized ongoing trials in this field (NCT01172990 and NTR3861).

In the meantime, it seems most reasonable to perform coronary angiography between 2 and 24 hours in NSTE-ACS patients selected for an invasive strategy.

**FUTURE PERSPECTIVE**

Guidelines and risk scores treat management of NSTEMI patients as a static process with several well-defined

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**Figure 3.** Exploratory meta-analysis of the incidence of early myocardial infarction in 7 randomized clinical trials assessing the timing of intervention in non-ST-elevation acute coronary syndromes. The studies are presented as “name, year of publication [reference]” and broken down into early versus delayed invasive management (1.1.1) and early versus urgent invasive management (1.1.2). In-hospital myocardial infarction was used for LIPSIA-NSTEMI; 30-day myocardial infarction was used for all other trials. Analyses were conducted assuming a random-effects model. Fixed-effects model analysis yielded similar results. Heterogeneity across studies was tested with Cochran’s Q statistic and the I² statistic. Analyses were conducted using Review Manager version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early invasive</th>
<th>Urgent/delayed invasive</th>
<th>Total</th>
<th>Weight</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.1 Early versus delayed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA, 2003 [73]</td>
<td>7</td>
<td>109</td>
<td>6</td>
<td>111</td>
<td>7.3%</td>
<td>1.20 [0.93, 1.57]</td>
</tr>
<tr>
<td>ISAR-CCOL, 2003 [74]</td>
<td>12</td>
<td>203</td>
<td>21</td>
<td>207</td>
<td>14.2%</td>
<td>0.56 [0.27, 1.16]</td>
</tr>
<tr>
<td>TIMACS, 2009 [72]</td>
<td>57</td>
<td>1593</td>
<td>69</td>
<td>1462</td>
<td>20.7%</td>
<td>0.97 [0.61, 1.56]</td>
</tr>
<tr>
<td>ELISA-3, 2013 [75]</td>
<td>5</td>
<td>299</td>
<td>2</td>
<td>301</td>
<td>3.7%</td>
<td>2.49 [0.48, 12.95]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2174</td>
<td>2621</td>
<td>88</td>
<td>2709</td>
<td>55.6%</td>
<td>0.68 [0.30, 1.52]</td>
</tr>
<tr>
<td>Total events</td>
<td>81</td>
<td></td>
<td></td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; CH² = 3.28, df = 3 (P = 0.36); I² = 8%
Test for overall effect: Z = 0.86 (P = 0.39)

<table>
<thead>
<tr>
<th>1.1.2 Early versus urgent</th>
<th>Early invasive</th>
<th>Urgent/delayed invasive</th>
<th>Total</th>
<th>Weight</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMA, 2009 [79]</td>
<td>25</td>
<td>99</td>
<td>44</td>
<td>73</td>
<td>15.0%</td>
<td>0.80 [0.25, 0.78]</td>
</tr>
<tr>
<td>ABOARD, 2009 [78]</td>
<td>6</td>
<td>177</td>
<td>15</td>
<td>176</td>
<td>11.0%</td>
<td>0.47 [0.25, 0.91]</td>
</tr>
<tr>
<td>LIPSIA-NSTEMI, 2012 [80]</td>
<td>17</td>
<td>200</td>
<td>27</td>
<td>200</td>
<td>17.2%</td>
<td>0.60 [0.31, 1.13]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>446</td>
<td></td>
<td>448</td>
<td>444</td>
<td>44.2%</td>
<td>0.48 [0.33, 0.72]</td>
</tr>
<tr>
<td>Total events</td>
<td>51</td>
<td></td>
<td></td>
<td>87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; CH² = 0.72, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)

<table>
<thead>
<tr>
<th>1.1.2 Early versus urgent</th>
<th>Early invasive</th>
<th>Urgent/delayed invasive</th>
<th>Total</th>
<th>Weight</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>2620</td>
<td></td>
<td>2469</td>
<td>100.0%</td>
<td>0.87 [0.49, 0.93]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.06; CH² = 8.52, df = 6 (P = 0.20); I² = 30%
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: CH² = 4.11, df = 1 (P = 0.04), I² = 75.7%
steps that occur in a chronological order (i.e. admission, diagnosis and risk stratification, treatment, discharge). Real clinical practice is, however, far more dynamic. The risk of an individual patient may change substantially during hospitalization due to events such as recurrence of angina or the unexpected angiographic finding of severe coronary disease. Surely, we will never be able to fully model the challenges of clinical medicine, but future adaptive risk models that allow for addition of new information during the course of hospitalization may provide more accurate and flexible therapeutic guidance. Troponin and novel biomarkers may play a substantial role in this development as it has recently been shown that they may be used to tailor antiplatelet therapy.\textsuperscript{87} Along this line, further development and application of high-sensitivity point of care biomarker assays will help to shift initial risk stratification and pharmacological pretreatment to the prehospital setting.\textsuperscript{88,89} High-risk NSTEMI patients can then be referred directly to a PCI-capable center to shorten delay to treatment without jeopardizing the 2-hour pharmacological pretreatment window that seems to be required to stabilize plaque and optimize outcome in these patients. In fact, the first steps towards such an approach are being taken in an ongoing prospective observational study (NTR4205).\textsuperscript{206}
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WEBSITES

201.GRACE risk score online calculator: http://www.outcomes-umassmed.org/grace/.

202.TIMI risk score online calculator: http://www.timi.org/.

203.CRUSADE bleeding score online calculator: http://www.crusadebleedingscore.org/.


206. The Netherlands Trial Register: http://www.trialregister.nl/.